

Public Assessment Report

Scientific discussion

**Acetylcysteine Alpex 600 mg,
effervescent tablets**

(acetylcysteine)

NL/H/3949/001/MR

Date: 8 June 2017

This module reflects the scientific discussion for the approval of Acetylcysteine Alpex 600 mg, effervescent tablets. The procedure was finalised on 12 April 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Acetylcysteine AlpeX 600 mg, effervescent tablets from AlpeX Pharma (UK) Limited.

Acetylcysteine is indicated for use as a mucolytic in respiratory disorders such as in bronchitis, emphysema, mucoviscidoses and bronchiectasis. Acetylcysteine AlpeX 600 mg, effervescent tablets is indicated in adults only.

A comprehensive description of the indications and posology is given in the SmPC.

This mutual recognition procedure concerns an application claiming essential similarity with the innovator product Fluimucil 600 mg effervescent tablets (NL License RVG 12151) which has been registered in the Netherlands by Zambon Nederland B.V. since 7 July 1987.

The concerned member states (CMS) involved in this procedure were Ireland and the UK.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Acetylcysteine AlpeX 600 mg are round, flat, white to yellowish tablets.

The effervescent tablets are packaged in a propylene tube with a polyethylene cap and a desiccant.

The excipients are: sodium hydrogen carbonate (E500), citric acid (E330), sucralose (E955), orange flavour (contains orange essential oil, orange essential oil terpenless, gum arabic (E414), butylhydroxyanisole (E320), citric acid monohydrate (E330) and maltodextrin (DE19)).

II.2 Drug Substance

The active substance is acetylcysteine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water. The polymorphic form of the drug substance is consistent and identical to the USP Reference Standard. Furthermore, the MAH has demonstrated that differences in particle size of the drug substance do not affect the dissolution behaviour.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The MAH has adopted the Ph. Eur. specifications and analytical methods plus additional specifications for microbial purity and particle size. The specifications are acceptable.

Batch analytical data demonstrating compliance with the drug substance specification have been provided. All three batches from both drug substance sources comply with the specifications.

Stability of drug substance

For one CEP holder stability data on the active substance have been provided for nineteen production scale batches stored at 25°C/60% RH (up to 72 months) and nine production scale batches stored at 40°C/75% RH (6 months). All parameters remain relatively stable and well within specifications at both conditions. Based on the provided stability data a re-test period of 5 years and the storage condition "Store in original package to protect from light" can be granted.

For the other manufacturer the re-test period of the substance is 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Several compositions and manufacturing methods have been tested. Wet granulation was chosen as the commercial manufacturing method.

Sufficient information with respect to the composition and the safety of the orange flavour has been provided. Comparative dissolution studies were conducted between Acetylcysteine AlpeX and the reference product Fluimucil 600 mg at pH 1.2, 4.5 and 6.8. These studies provided confirmation that the solubility characteristic of Acetylcysteine AlpeX effervescent tablets is not influenced by the pH of the medium and that the amount of active substance in the solution to be administered is equivalent to that of reference product. No bioequivalence studies have been performed since the MAH applied for a biowaiver. The data included in the dossier is sufficient to support a biowaiver in accordance with Guideline on the Investigation of Bioequivalence.

Manufacturing process

The manufacturing method is a wet granulation process and consists of granulation, sieving, mixing and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial-scale batches. The manufacturing process has been adequately described and validated. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with either the Ph.Eur., the USP/NF or - for orange flavour - in-house specifications. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, degradation, appearance of solution, pH, disintegration time, average weight, uniformity of dosage units, loss on drying, and microbiological quality. A shelf-life specification on hardness is applied.

Batch analytical data from the proposed production site have been provided on three batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three commercial scale batches stored at 25°C/60%RH (36 months), 30°/75%RH (24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a polypropylene tube with a polyethylene cap and desiccant with 6, 10 or 20 tablets per tube.

The stability results show that no changes are observed (with the exception of some analytical variance) under all storage conditions and for all parameters tested. Also the in-use stability study of both tablet strengths did not show significant changes in any of the examined parameters.

On the basis of extrapolation of the submitted data a shelf-life of 36 months can be granted, if stored in the original container to protect from moisture.

Stability data has been provided demonstrating that the product remains stable for a maximum of 10 days for the 6 and 10 tablets tube and for a maximum of 20 days for the 20 tablets tube following first opening of the container.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Acetylcysteine Alpex has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to submit a risk assessment of the potential presence of elemental impurities within the ICH deadline.
- The MAH committed to submit the report of a 3 months in-use stability study compliant to CPMP/QWP/2934/99.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Acetylcysteine Alpex is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Flumucil effervescent tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Acetylcysteine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

This is a generic application for Acetylcysteine Alpex effervescent tablets referring to Flumucil effervescent tablets as reference medicinal product. The N-acetylcysteine effervescent tablets are dissolved in water before administration. Therefore, the test product is administered as an aqueous solution, at the same concentration of active substance as the innovator product. The excipients used for production of Acetylcysteine Alpex 600 mg do not affect gastrointestinal transit, absorption, *in-vivo* solubility and stability of the active substance. Therefore, an exemption from *in-vivo* bioequivalence study is acceptable, in accordance with the guideline on the investigation of bioequivalence CPMP/EWP/ QWP/1401/98/Rev1.

IV.3 Clinical efficacy and safety

The indication initially applied for was 'treatment of disorders of the airways in which a reduction in the viscosity of bronchial secretions is required to facilitate expectoration, such as in asthma, bronchitis, emphysema, mucoviscidosis and bronchiectasis in adults.'

During the procedure, following comments of the member states, the company changed the indication into ‘use as a mucolytic in respiratory disorders such as in bronchitis, emphysema, mucoviscidoses and bronchiectasis. Acetylcysteine Alpex 600 mg, effervescent tablets is indicated in adults *only*.’

Based provided literature in the clinical overview, the efficacy and safety in adults is sufficiently justified. The removal of asthma from the indication is considered acceptable as per GINA (Global Initiative for Asthma) the use in the treatment of asthma is not supported.

There are no data for acetylcysteine 600 mg that support the use in a population younger than 18 years in the proposed indication. There are also no pharmacokinetic trials comparing acetylcysteine 3 x 200 mg and 1 x 600 mg. The known safety profile in adults cannot be extrapolated without any supportive (pharmacokinetic) data.

Furthermore, the risk of suffocation in children < 2 years of age because of the abundant mucus is addressed as a contra-indication in line with the innovator. The efficacy and safety of acetylcysteine 600 mg is not established in the remaining age group of the paediatric population, i.e. children from 2 years of age and adolescents. However, the use in this age group is not considered a contraindication; other forms and strengths of acetylcysteine are more suitable for children > 2 and adolescents.

Acetylcysteine can be used as mucolytic in patients suffering from bronchitis and COPD. However, it is not always clear to make a distinction between asthma and chronic bronchitis/COPD. In patients with asthma, acetylcysteine may have an increased risk of bronchospasm. As patients and physicians should be advised about this risk, a warning has been added to the SmPC: ‘Bronchospasms may occur with the use of acetylcysteine. If bronchospasms occur, the medicinal product should be discontinued immediately.’

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Acetylcysteine Alpex.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> • Safety in children aged < 2 years • Severe hypersensitivity reactions (including anaphylactic shock)
Important potential risks	<ul style="list-style-type: none"> • Severe skin reactions (including Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) • Clinical effects resulting from anticoagulant and platelet-inhibiting properties of acetylcysteine
Missing information	<ul style="list-style-type: none"> • Use in pregnant and lactating women

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Fluimucil. No new clinical studies were conducted. Acetylcysteine Alpex 600 mg, effervescent tablets are considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of the reference product. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with

5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Acetylcysteine Alpex 600 mg, effervescent tablets has a proven chemical-pharmaceutical quality and is a generic form of Fluimucil 600 mg effervescent tablets. Fluimucil is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are administered as an aqueous solution, at the same concentration of active substance, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors. Acetylcysteine Alpex 600 mg, effervescent tablets was authorised in the Netherlands on 29 October 2014.

There was no discussion in the CMD(h) during the MRP. Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, mutually recognised the MEB's evaluation for marketing authorisation. Essential similarity has been demonstrated for Acetylcysteine Alpex with the reference product. The mutual recognition procedure was finalised with a positive outcome on 12 April 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached